Antimicrobial Stewardship Management of Infections:

Beyond the Costs of Antimicrobials

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Antimicrobial resistance is a global problem,[1] and antimicrobial stewardship programs (ASPs) are the global solution. Both national and international organizations are recognizing the growing importance of ASPs and are fostering their development through symposia, workshops, and/or certification programs dedicated to ASP (Table 1).

During the past decade, the prevalence of ASPs at US hospitals has greatly increased, and the state of California now mandates that general acute care hospitals develop a program to evaluate the judicious use of antibiotics.[2] Additionally, the Infectious Diseases Society of America (IDSA) has made recommendations to the Centers for Medicare & Medicaid Services (CMS) to require stewardship in all acute care hospitals in the United States as part of infection control.[3] To spur stewardship efforts, the Joint Commission's 2012 National Patient Safety Goals include 2 goals relevant to ASP: Get important test results to the right staff person on time and foster hand hygiene compliance to prevent infections.[4]

The goal of antimicrobial stewardship is to optimize antimicrobial therapy for improved patient outcomes, with maximal effect on subsequent development of resistance.[5] The changing landscape of health care reform places increasing pressure on ASPs to use the most cost-effective antimicrobial to decrease expenses. Cost usually plays a major role in the formulary decision process when ASPs examine targeted antimicrobial agents that have similar efficacy and safety. ASPs face

Table 1. US and International Organizations With Programs Fostering ASPs

National Organizations	International Organizations
Making a Difference Infectious Diseases	European Congress of Clinical Microbiology and Infectious Diseases
Society of Infectious Diseases Pharmacists	International Congress Antimicrobial Agents and Chemotherapy
Society of Healthcare Epidemiology	Federation of Infectious Diseases Societies of South Africa
Infectious Diseases Association of California	
Infectious Diseases Society of America	

ASPs, antibiotic stewardship programs

additional pressures due to the lack of new therapeutic choices. New antibiotic development is at a standstill, in part because antibiotics are not as profitable as other drugs.[6] Moreover, once a new antibiotic makes it to the market, ASPs commonly hold it "in reserve" due to fear of drug resistance, as well as fear of the economic effect on the ASP budget. ASPs also face the challenge of being considered "cost centers" and not "revenue generators" by health-system administrators.[7]

However, there is increasing realization that one of the highest expenses in infection management is the cost of failure or relapse; this is compounded by the added intangible negative effect of patient dissatisfaction and hospital readmission. Reducing readmissions is considered by many in the policy world to be "low-hanging fruit."[8,9] In an attempt to capitalize on this, the Affordable Care Act has provisions to improve performance on 30-day Medicare readmission rates for pneumonia and other diseases.[10] Hospitals will be assessed a payment penalty for higher than expected readmission rates effective Oct. 1, 2012. Thus, reducing readmissions likely will become an additional focus of stewardship programs.

The Ohio State University Wexner Medical Center (OSUWMC) ASP is based on the concept that appropriate antimicrobial selection should result in the most rapid resolution of the infection, shorten hospital length of stay (LOS), reduce the risk for developing resistant pathogens, and improve morbidity and mortality but that it may increase pharmacy charges.[11] Recognizing that a business model emphasizing improved efficiency of care may be the optimal way to support ASP, this paper describes a disease-based approach to stewardship rather than a drug-based approach. The management of 4 types of infection—multidrug-resistant gram-negative infections, staphylococcal bacteremia, candidemia, and *Clostridium difficile* infection (CDI)—are discussed from a stewardship perspective.

Stewardship Checklist

If one of the goals of an ASP is to improve patient outcomes while being fiscally responsible, a coordinated effort by all ASP team members (physicians, pharmacists, microbiologists, epidemiologists, infection preventionists, and data managers) is necessary. The figure shows OSUWMC's ASP model. Table 2 is a checklist of ASP initiatives. It incorporates key stewardship concepts and specific roles for all team members and can be used by both fully staffed programs as well as those with limited resources.

Infection-Prevention Strategies

Infection prevention uses scientifically proven concepts—such as tracking resistance trends, applying infection control practices and, importantly, sharing information with staff—to achieve its goals (Table 3). Communicating and collaborating with infection preventionists is critical to the success of an ASP. The best antibiotic for a patient is of little value, if health care workers do not clean their hands and risk cross-transmission to other patients. Lack of compliance with hand hygiene, contact isolation, and meticulous environmental cleaning contributes to the spread of multidrug-resistant organisms from one patient to the next.

Microbiology

Another strategy ASPs can use is rapid diagnostic tests to identify antimicrobial-resistant bacteria. Infectious Diseases Society of America past president John Bartlett, MD, called the advent of these tests a "game changer" in infectious disease.[12] One of the first stewardship papers to apply such tests with infectious disease pharmacist stewardship interventions demonstrated a shorter time to initiation of pathogen-specific therapy when the tests were used to differentiate methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), and coagulase-negative staphylococci (CoNS).[13] There are now several rapid diagnostic tests using different methods to detect *S. aureus* and CoNS. These include peptide nucleic acid fluorescence in situ hybridization (PNA-FISH), polymerase chain reaction (PCR) assays, bacteriophage amplification-based assays, and nucleic acid tests to detect genes specific to *S. aureus* and *S. epidermidis*. Additional tests with PNA-FISH technology are available to detect *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Candida* species from positive blood cultures. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF) is another rapid diagnostic that is just starting to be used in the United States. As more

Table 2. ASP Infection Management Initiatives

	Ideal ASP Team	Limited-Resource ASP Team
Infection Preventionist		
Hand hygiene	✓	✓
Contact isolation	✓	✓
Environmental cleaning • High-touch surfaces	✓	✓
Computer decision support and alerts • Identification of high-risk patients • Microbial results to infection preventionist • Track and trend transmissible pathogens	✓	
Microbiologist		
Antibiogram (hospital-wide) • Unit specific • Combination	✓ ✓ ✓	✓
Rapid diagnostic tests • rPCR, Quick-FISH, nucleic acid test, bacteriophage amplification, MALDI-TOF • Communicate results to pharmacist	✓ ✓	 ✓
Pharmacist/Physician		
Dose optimization • Extended- or continuous-infusion β-lactams • Renal dose adjustments • Drug level monitoring	✓ ✓ ✓ ✓	✓ ✓ ✓ ✓
"Antibiotic hang time"	✓	✓
Core measures • CAP • SCIP	 ✓ ✓	 ✓ ✓
Computer decision support • Bug–drug mismatch • Duplicate therapy • Results to ASP	✓ ✓ ✓ ✓	
Education • One on one • Patient care rounds • Grand rounds • Hospital ASP Web site • Medical apps (eg, iPhone or iPad)	✓ ✓ ✓ ✓ ✓ ✓	✓ ✓ ✓ ✓
Clinical outcomes • LOS • Infection-related LOS • Mortality • 30-day readmissions for MRSA bacteremia, *C. difficile*, CAP, and SSIs	 ✓ ✓ ✓ ✓	 ✓ ✓ ✓

ASP, antimicrobial stewardship program; **CAP,** community-acquired pneumonia; **FISH,** fluorescence in situ hybridization; **LOS,** length of stay; **MALDI-TOF,** matrix-assisted laser desorption/ionization–time of flight; **MRSA,** methicillin-resistant *Staphyloccocus aureus*; **rPCR,** rapid polymerase chain reaction; **SCIP,** surgical care improvement project; **SSI,** surgical site infection

Table 3. Infection-Prevention Strategies

- Identify occurrences and trends of MDROs such as MRSA, *Acinetobacter baumannii*, ESBL-producing organisms, and *Pseudomonas aeruginosa*
- Apply practices to prevent transmission of MDROs to other patients:
  - -Use reminders, accountability, and corrective action, if necessary to stress the importance of hand hygiene before and after each patient contact
  - -Isolate patients in private rooms, as feasible, with health care workers wearing a gown and gloves; and re-isolate patients with epidemiologically significant organisms to your organization
  - -Ensure surfaces and equipment are appropriately disinfected to reduce potential spread
  - -Bathe patients with antiseptic soap
  - -Decolonize patients of *S. aureus* if they are to undergo high-risk surgical procedures
  - -Provide education to patients and family members about the MDRO
  - -Communicate the infection to all health care providers (ie, other health care institutions, ambulatory sites)
- Implement care bundles: universal protocol, checklists, and internal practice guidelines that when consistently used, reduce the risk for surgical site- and device-related infections
- Share trends about hand hygiene and MDRO-related infections with clinical staff, ASP members, and administrative leadership to improve and share opportunities for control

ESBL, extended-spectrum β-lactamase; **MDRO,** multidrug-resistant organism; **MRSA,** methicillin-resistant *Staphylococcus aureus*

ASPs incorporate rapid diagnostics, the clinical effect of implementation of such tests on patient care, specifically reduced time to effective therapy, can be realized.

Clinical Outcomes

ASPs have the opportunity to affect several clinical outcomes of infected patients, including the time to effective therapy, optimized dosing, and duration of therapy.

Time to Effective Therapy

Tools to shorten the time to delivery of appropriate initial therapy are key components of ASPs. Kumar et al found that initiation of effective antimicrobial therapy within the first hour after the onset of hypotension in patients with septic shock was associated with improved survival.[14] For every additional hour to effective antimicrobial initiation during the first 6 hours after hypotension onset, survival dropped an average of 7.6%. ASPs should evaluate antimicrobial "hang time"—defined as the time from physician order entry to the time the nurse actually hangs the IV antimicrobial. If excess hang time is not addressed, the opportunity to improve patient outcomes may not be realized. As Dr. Kumar's study demonstrates, every hour counts.

Optimized Dosing

Vancomycin has been considered the drug of choice for MRSA bacteremia. Pharmacists have traditionally provided vancomycin therapeutic drug monitoring as the standard of care. In addition to monitoring of drug levels, ASPs also should evaulate whether vancomycin is the most appropriate anti-staphylococcal agent for patients with MRSA bacteremia. High rates of vancomycin failure in MRSA infections increasingly are being reported.[15] Kullar et al identified several independent predictors of vancomycin failure, including 2 that can be addressed by ASPs—an initial vancomycin trough less than 15 mg/L and a vancomycin minimum inhibitory concentration (MIC) greater than 1 mg/L by Etest. Consensus guidelines recommend considering use of alternative agents for infections involving a higher vancomycin MIC.[16] A recent study compared vancomycin with daptomycin (Cubicin, Cubist) for the treatment of patients with MRSA bacteremia with a high vancomycin MIC (>1 mg/L) and found a higher probability of survival among those in the daptomycin-treated group (P=0.022).[17]

Treatment of gram-negative infections often includes the use of β-lactam antimicrobials. In vitro and animal studies have demonstrated that the best predictor of bacterial killing is the time during which the free-drug concentration exceeds the MIC of the organism.[18]

ASPs may be able to optimize the pharmacodynamics of first-line anti-pseudomonal β-lactam antibiotics by implementing extended infusions of β-lactam antibiotics such as piperacillin/tazobactam, cefepime, meropenem, and doripenem (Doribax, Janssen). Improved outcomes have been documented by administering extended-infusion β-lactam therapy to critically ill patients with *P. aeruginosa* infections.[19] An initial assessment of the hospital's MIC for *P. aeruginosa* should be done to determine if extended infusion β-lactams provide value; this may not be necessary if *P. aeruginosa* isolates have low MICs.

Reduce Duration of Antimicrobials

Reducing the length of antibiotic courses is the strategy most likely to be effective in reducing antibiotic

resistance.[20] Hayashi et al reviewed several strategies and results from clinical trials that used short-course therapy for reduction in duration of antimicrobials.[21] Use of biomarkers such as procalcitonin in conjunction with clinical signs of resolution of infection can assist ASPs in efforts to de-escalate or discontinue antimicrobials.

Hospital LOS and antibiotic-related LOS are important parameters for ASPs to monitor. Bauer et al documented that when ID pharmacist interventions resulted in shorter time to optimal antibiotic therapy for patients with bacteremia, LOS also was decreased.[13] Considering that LOS is the most expensive component of hospitalization, ASPs should monitor the relationship of interventions to LOS in addition to the antimicrobial budget to remain fiscally responsible over the long term.

Targeted Management of Resistant Organisms

The following sections focus on prevalent resistant organisms and strategies to best manage patients infected with these organisms while reducing resistance.

Extended-spectrum β-Lactamase–producing Enterobacteriaceae

Epidemiology

Infections caused by resistant bacteria expressing extended-spectrum β-lactamase (ESBL) pose serious challenges to clinicians. These organisms are increasingly identified, having become endemic in many hospital settings and also are reported as causes of community-acquired infections. *E. coli* and *K. pneumoniae* are the most frequently identified ESBL-producing organisms.

Clinical and Economic Outcomes

The presence of ESBL-producing organisms has demonstrated an association with unfavorable patient outcomes. Studies comparing outcomes between ESBL-associated versus non–ESBL-associated *Enterobacteriaceae* bacteremia show that ESBL production is an independent predictor of delay in initiation of appropriate therapy, LOS, mortality, and cost.[22] An important reason associated with poor outcomes is the presence/acquisition of multiple resistance mechanisms, which decreases therapeutic options. A report from the IDSA emphasized the lack of available antimicrobials for drug-resistant organisms.[23]

In the treatment of ESBL-producing organisms, carbapenems are associated with a high rate of clinical and microbiologic success. In one study, 96% of patients who received a carbapenem-containing regimen had a favorable response or were cured.[24] In a retrospective study of consecutive patients, those treated with imipenem for an ESBL-producing bacteremia were significantly more likely to survive than were patients treated with a cephalosporin.[25]

Antimicrobial Stewardship

ASPs should track the rates of ESBL-producing organisms annually. OSUWMC's ASP recently joined SMART (Study for Monitoring Antimicrobial Resistance Trends), a global surveillance program designed to longitudinally monitor the epidemiologic trends and in vitro antimicrobial activity of 12 antimicrobials against a variety of aerobic and facultative gram-negative bacilli isolated from patients. This allows a stewardship program to benchmark resistance rates to other US hospitals in addition to hospitals worldwide.

Microbiology laboratories should use the recently lowered Clinical Laboratory Standards Institute (CLSI) breakpoints or confirm the presence of ESBL activity. If an isolate is confirmed as an ESBL producer, the microbiology laboratory should report all penicillins, cephalosporins, and aztreonam as resistant. Consideration should be given to reporting only carbapenems as options for treatment of blood isolates. At the time of ESBL identification, the microbiology laboratory also should prompt the clinician to place a contact isolation order because appropriate infection control can decrease the potential risk of ESBL cross transmission. Additionally, stewardship programs should consider limiting the use of third-generation cephalosporins through prior authorization or prospective feedback and education.

Acinetobacter baumannii

Epidemiology

Over the past 3 decades, *A. baumannii* has emerged from being an organism of questionable pathogenicity to an infectious agent of great importance in hospitals worldwide.[26,27] Multidrug-resistant *A. baumannii* is recognized as being among the most difficult organisms to control and treat. Risk factors for infection include an ICU stay, recent surgery, central vascular catheterization, mechanical ventilation, and treatment with third-generation cephalosporins, fluoroquinolones, or carbapenems.[28,29]

Clinical and Economic Outcomes

A. baumannii is associated with both outbreaks and health care–associated infections (HCAIs) and demonstrates high morbidity, mortality, and costs.[30-32] A retrospective, matched cohort study found that patients with *A. baumannii* infection had a 5-day excess length of mechanical ventilator dependence and ICU stay compared with other critically ill patients without this infection. Additionally, *A. baumannii* infections are associated with an overall mortality rate between 26% and 68%.[30]

Antimicrobial Stewardship

Infection control for *A. baumannnii* is paramount to prevent cross transmission and additional development of resistance. Because of the prevalence of resistant organisms, including *A. baumannii*, in long-term care facilities, institutions should consider placing patients transferred from high-risk locations into contact plus/minus droplet isolation until the presence of *A. baumannnii* is ruled out. Surveillance cultures may be obtained if patients were previously colonized or infected. Early recognition is important to avoid inadvertent cross transmission and aggressively control potential spread. Additionally, meticulous daily cleaning

of frequently used surfaces is an important intervention. ASPs must ensure that staff optimize hand hygiene, comply with contact isolation for colonized or infected patients, and use dedicated medical equipment. For hospitals with limited resources for surveillance of hand-hygiene adherence, a free medical application (iScrub) is available to download from the Apple App store to an iPhone or iPad.[33] This allows any health care worker to record observations and electronically transmit the data to a hospital epidemiologist.

A. baumannii also represents many challenges from a microbiology perspective because the organism can be difficult to identify using conventional microbiology methods. Novel technology, including MALDI-TOF has been used extensively in Europe and is being applied in the United States. This technology allows for the rapid identification of organisms from cultures (respiratory, blood, or wound) within minutes versus conventional methods that take at least 24 hours. With rapid organism identification, patients may receive earlier, targeted therapy, which is of great importance for *A. baumannii*, because it is becoming increasingly resistant.

A. baumannii is intrinsically resistant to commonly used antibiotics, including aminopenicillins and first- and second-generation cephalosporins. *A. baumannii* has remarkable capacity to acquire mechanisms conferring resistance.[34] Antimicrobials with activity against *A. baumannii* include ampicillin/sulbactam, colistin, carbapenems (doripenem, imipenem, and meropenem), minocycline, and tigecycline (Tygacil, Wyeth). In many hospitals, only colistin provides reliable activity. The microbiology laboratory must confirm susceptibility testing by completing Etests for colistin, minocycline, and tigecycline.

OSUWMC's ASP reviewed minocycline for the treatment of infections due to *A. baumannii*. The microbiology laboratory performed susceptibility testing and determined that minocycline was an option in the treatment of multidrug-resistant *A. baumannii*. Among the isolates resistant to imipenem and ampicillin/sulbactam, 18 of 47 isolates (38%) were susceptible to minocycline; the ASP recommended minocycline for formulary addition. OSUWMC's early experience treating 5 *A. baumannii*–infected patients showed that all 5 had microbiologic eradication from blood and respiratory sites and all but 1 patient were successfully treated.[35]

Pseudomonas aeruginosa

Epidemiology

P. aeruginosa infections constitute a tremendous burden on hospitals in terms of morbidity, mortality, and health care costs. Studies have demonstrated that *P. aeruginosa* infections are associated with a mortality rate of 18% to 60% and that the cost of treatment is substantial, ranging from $20,000 to $80,000.[36-41] *P. aeruginosa* infections continue to present unique challenges to ASPs because *P. aeruginosa* is associated with multiple resistance mechanisms and poor patient outcomes.

Clinical and Economic Outcomes

Carmeli et al examined the clinical and economic outcomes of patients with *P. aeruginosa*. The emergence of resistance was associated with severe adverse outcomes, including a 3-fold increase in mortality and a 2.1-fold increase in hospital LOS.[42] The most important reason for the substantial mortality was the delay in starting effective antimicrobial therapy and inadequate empiric choices based on resistance. The marked escalation in the prevalence of resistance in *P. aeruginosa* has made the selection of empiric antimicrobial therapy increasingly complex.[43]

Antimicrobial Stewardship

P. aeruginosa is one of the most important organisms for ASP to address because most empiric antimicrobial prescribing is directed toward patients with risk factors for or confirmed infections with *P. aeruginosa*. Combination therapy may be prescribed until the infecting organism and susceptibilities are available; this time frame often leads to prolonged, unnecessary antimicrobial use. Rapid techniques are now available for identification of *P. aeruginosa*. One of these technologies, Gram-Negative Rod (GNR) Traffic Light® PNA Fish® (AdvanDx) provides identification of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* directly from GNR-positive blood cultures in 90 minutes.[44] A second technology, MALDI-TOF, also can provide rapid identification from a variety of culture sites, not just blood cultures. These technologies that allow more rapid identification result in patients receiving earlier, targeted therapy, which can lead to more rapid de-escalation of additional antimicrobials.

The selection of empiric therapy is based in large part on the susceptibility rates compiled from an institution's antibiogram. Unfortunately, institution-wide antibiograms may fail to reveal important differences in susceptibility data across specific patient-care units, particularly in ICUs within an institution.[45] These unit-specific differences are critical to the selection of the optimal regimen and the tracking of emerging patterns of resistance because certain patient types (ie, trauma patients, sepsis patients) and those with mixed disease states are admitted to distinctly different types of units. At OSUWMC, Clinical Epidemiology and Microbiology create ICU-specific antibiograms annually. The data in these antibiograms were invaluable to help identify a then-unknown ESBL outbreak in 2000 and to assess the utility of using fluoroquinolones in specific ICUs in 2011. Hospital-wide and unit-specific antibiograms help ASPs select the optimal regimen for patients at risk for infections with *P. aeruginosa* and track unit-specific resistance rates. Combination antibiograms to assess any potential advantage for combination empiric treatment of *P. aeruginosa* also are now completed annually.

P. aeruginosa's multiple resistance mechanisms result in higher MICs and, combined with a lack of newer antibiotics in the pipeline, leave ASPs in search of optimal doses to potentially overcome resistance.[46] ASPs must recommend the available agents to achieve optimal outcomes, minimize collateral damage, and prevent

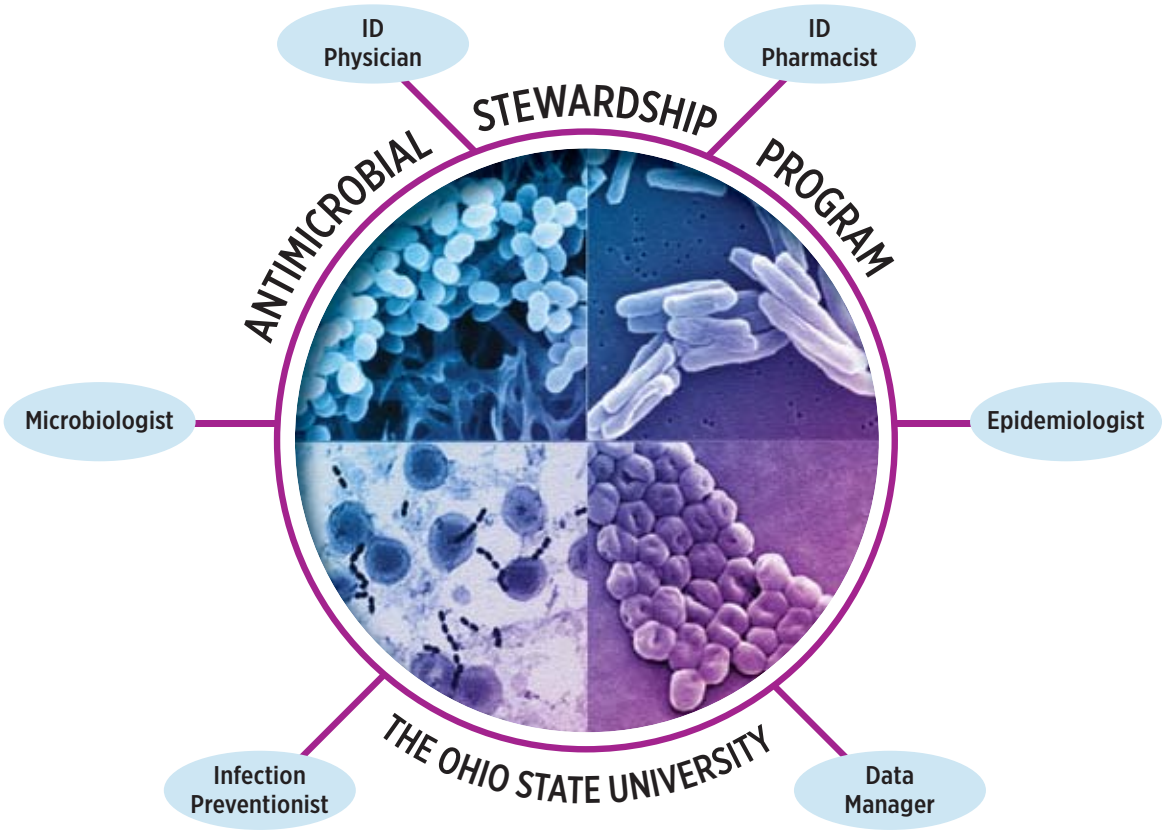

Figure. OSUWMC ASP model.

ASP, antimicrobial stewardship program; **ID,** infectious diseases; **OSUWMC,** Ohio State University Wexner Medical Center

inappropriate therapy (ie, continuing anti-pseudomonal therapy when the organism is not identified). Historically, β-lactams are administered via intermittent infusion; this results in high peak concentrations that do not enhance bactericidal activity, but during the dosing interval, concentrations may fall below the MIC.[18,47,48] The approved dosing regimens for β-lactams worked reasonably well in the past, but with escalating resistance, these regimens may fail to optimize pharmacodynamics, resulting in suboptimal patient outcomes.

Lodise et al evaluated extended-infusion piperacillin/tazobactam in patients with *P. aerguinosa* infections. Among patients with an APACHE II score of 17 or higher, 14-day mortality was significantly lower among those who received extended-infusions (12.2% vs 31.6%; P=0.04).[19] Extended-infusion cefepime also has been evaluated in the treatment of *P. aeruginosa* infections. In a prospective, observational evaluation of adult patients with ventilator-associated pneumonia (VAP), Nicasio et al demonstrated that cefepime 2 g every 8 hours infused over 3 hours provided the highest probability of target attainment using pharmacodynamic modeling. The study demonstrated a significant decrease in infection-related LOS (11.7±8.1 vs 26.1±18.5 days; P<0.001).[49]

OSUWMC infuses all broad-spectrum β-lactams (ie, piperacillin/tazobactam, cefepime, and doripenem) over 4 hours, after the first dose is ordered "stat" and infused over 30 minutes. Compliance with extended infusion is documented to be approximately 95%. OSUWMC's ASP recently completed a study evaluating the clinical and economic outcomes associated with extended-infusion cefepime. Overall mortality was significantly lower in the patients receiving an extended infusion compared with those receiving an intermittent infusion.[50] Institutions should consider obtaining exact MICs on all gram-negative isolates to determine the optimal antimicrobial agent, regimen, and infusion time.

MRSA Bacteremia

Epidemiology

MRSA infections are a significant concern due to their high propensity to increase morbidity, mortality, and health care costs. MRSA has become an increasingly important pathogen in both community and nosocomial infections over the past 2 decades, particularly in ICUs. Approximately 60% of *S. aureus* nosocomial

infections occurring among patients in the ICU are caused by MRSA.[51]

Clinical and Economic Outcomes

Bacteremia with MRSA has been reported to be associated with mortality rates between 15% and 60%. Treatment for MRSA bacteremia is substantial, with costs ranging from $20,000 to $70,000 per episode.[52,53] The problem of MRSA bacteremia has escalated to the point that US Department of Health and Human Services made MRSA infections 1 of the 6 categories of HCAIs in its 5-year National Prevention Targets.[10] In 2013, the management of MRSA bacteremia will be a national hospital quality measure and part of the value-based purchasing program.

Antimicrobial Stewardship

OSUWMC's ASP has taken considerable action in optimizing the diagnosis and management of *S. aureus* bacteremia. Recently, rapid polymerase chain reaction (rPCR) assays have been shown to improve clinical outcomes by decreasing the time to identification of *S. aureus*. The medical center's ASP evaluated the clinical effect of rPCR assays on clinical and economic outcomes. The microbiology laboratory contacted an ID pharmacist with results of the rPCR and the pharmacist recommended effective antibiotics and an ID physician consult. Mean time to switch from empiric vancomycin to cefazolin or nafcillin in patients with MSSA was 1.7 days shorter with the rPCR plus the ID pharmacist intervention versus without intervention (P=0.02). For MRSA bacteremia, vancomycin was considered to be effective unless the patient met the stewardship criteria for vancomycin failure, at which time daptomycin was recommended. In the post-rPCR group, daptomycin was recommended 5.5 days sooner in patients who met criteria for vancomycin failure. In this intervention group, the mean hospital LOS was 6.2 days shorter and the mean hospital costs were $21,387 less. Use of a rapid identification test and a stewardship pharmacist resulted in significantly improved clinical and economic outcomes.[13]

The optimal treatment of MRSA bacteremia continues to evolve. Vancomycin has been the mainstay of therapy for years. Recent reports have linked vancomycin-treatment failure with MRSA and susceptible vancomycin MICs of 1 to 2 mg/L.[54,55] As mentioned previously, recent consensus guidelines recommend that clinicians consider using alternative agents when the vancomycin MIC is greater than 1 mg/L.[16] Daptomycin is considered a reasonable alternative to vancomycin and is FDA-approved for the treatment of MRSA bacteremia, even in patients with right-sided endocarditis. A recent study evaluated the effectiveness and safety of vancomycin compared with those of daptomycin, in the treatment of patients with MRSA bloodstream infections (BSIs) with a high vancomycin MIC (>1 mg/L). Clinical failure, defined as mortality, microbiologic failure, and/or recurrence of infection, was lower in the daptomycin-treated group (31% vs 17%; P=0.084) and was mainly driven by a lower incidence of mortality in the daptomycin group (20% vs 9%; P=0.046). Factors independently associated with clinical failure included acute renal failure and vancomycin treatment.[17] This study supports recent guidelines recommending a switch to alternative therapy when the isolate has a high but susceptible MIC to vancomycin. In addition to daptomycin, ceftaroline (Teflaro, Forest) represents another therapeutic alternative. Ceftaroline is FDA-approved for the treatment of community-acquired pneumonia and acute bacterial skin and skin structure infections. In a recent study of ceftaroline as off-label salvage therapy for the treatment of MRSA bacteremia or endocarditis, 6 patients were successfully treated, experiencing rapid clearance after starting ceftaroline.[56] Additional studies are necessary to establish the role of ceftaroline in the management of MRSA bacteremia.

ASPs should consider completing Etests on MRSA bloodstream isolates to help determine the optimal antibiotic for the treatment of MRSA bacteremia. This methodology has demonstrated increased reliability for predicting treatment response.[57,58] Alternative therapy should be strongly considered for isolates with a vancomycin MIC of 1 to 2 mg/L. Stewardship programs should consider prospective auditing and feedback of daptomycin or ceftaroline or an ID physician consultation for all patients with MRSA bacteremia.

Candidemia and Invasive Candidiasis

Epidemiology

Hospitalizations complicated by candidemia have increased since 2000.[59] Candidemia represents the fourth most common cause of nosocomial bloodstream infections (BSIs) in the United States and results in significant morbidity, mortality, and hospital cost. Studies estimate attributable mortality rates as high as 50%.[60,61] Over the past decade, the epidemiology of BSI with *Candida* species has changed. There has been a global shift toward non-albicans *Candida* species, particularly *C. glabrata*.[62] This change in epidemiology is particularly concerning because *C. glabrata* displays dose-dependent fluconazole susceptibility, with resistance reported in as many as 23% of isolates.[63]

Clinical and Economic Outcomes

A recent review of 1,915 patients from 7 randomized trials for treatment of invasive candidiasis assessed the effect of host, organism, and treatment-related factors on clinical cure and mortality.[64] After evaluating numerous factors associated with outcomes, the investigators identified only 2 modifiable strategies to improve patient outcomes. Treatment with an echinocandin antifungal and removal of a central venous catheter (CVC) were associated with decreased mortality and greater clinical success. Patients who received an echinocandin—caspofungin (Cancidas, Merck), micafungin (Mycamine, Astellas), or anidulafungin (Eraxis, Pfizer)—had significantly better survival rates than patients who received either a polyene—amphotericin B, liposomal amphotericin B—or

a triazole—fluconazole, voriconazole (mortality, 27% for echinocandins vs 36% for other regimens; $P<0.0001$).

Arnold et al evaluated the effect of inadequate antifungal dosing or administration of an antifungal to which the isolate was resistant, on postculture hospital LOS and costs. Postculture LOS was shorter in the appropriate therapy group (7 vs 10.4 days; $P=0.037$) and correlated with total hospital costs that were lower in the appropriate therapy group ($15,832 vs $33,021; $P<0.001$).[65] Other studies have found the additional cost of each invasive candidiasis episode to be nearly $40,000.[60,61]

Antimicrobial Stewardship

The IDSA Clinical Practice Guidelines for the Management of Candidiasis published in 2009 suggest that early initiation of antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever. In cases of confirmed candidemia, the guideline focuses on CVC removal and rapid initiation of fluconazole or an echinocandin in non-neutropenic patients.[66] Echinocandins are recommended as a first-line choice for invasive candidiasis for the critically ill, those with prior triazole exposure, and those infected with less-susceptible *Candida* species, such as *C. glabrata* and *C. krusei*. Clinical application of these guidelines can be inconsistent which may result in suboptimal patient outcomes.[67,68]

Many ASPs may prefer to position fluconazole, rather than the echinocandins, as the first-line agent for empiric antifungal therapy due to its lower cost. However, in a recent study, Andes et al found the echinocandin class to be superior for both *C. albicans* and non-albicans groups and suggested that ASPs should re-evaluate the role of fluconazole as first-line therapy for patients with invasive candidiasis.[64]

The OSUWMC practice guideline lists an echinocandin (caspofungin) as the preferred agent for empiric antifungal therapy in patients with suspected invasive candidiasis. This approach minimizes delay to effective therapy for potential fluconazole-resistant *C. glabrata* and *C. krusei*, which have been identified at OSUWMC. A recommendation to de-escalate to fluconazole is made once the species and/or susceptibilities are known. OSUWMC's microbiology laboratory uses rapid molecular-based diagnostic methods to shorten the time to positive identification of yeast from blood cultures. The Yeast Traffic Light® PNA-FISH test was implemented by the center's ASP to assist in the management of candidemia.[44] The microbiology technician pages the ASP pharmacist with the PNA-FISH test results. This is crucial because others have shown that a delay in therapy (even as little as a few hours) is associated with increased mortality.[68,69] For this difficult group of patients, ASP pharmacists recommend removal of the CVC and consultation by ID physicians.

Clostridium difficile

Epidemiology

CDI is a common cause of health care–associated diarrhea. Symptoms range from mild diarrhea to pseudomembranous colitis to death. CDIs nearly always are associated with prior antibiotic exposure; ampicillin, clindamycin, third-generation cephalosporins and, more recently, quinolones are the most commonly identified drugs. Recurrences occur in 25% of patients.[70] Minimizing the frequency, number, and duration of antimicrobial therapy prescribed will reduce the risk for CDI, and ASPs are recommended.[71]

Clinical and Economic Outcomes

CDI has increased almost 4-fold over the past decade. An epidemic strain termed the North American Pulse Field Type 1 (NAP-1) with increased virulence and toxin production was reported from multiple outbreaks.[72] In 2009, 336,600 US hospitalizations involved CDI, representing nearly 1% of all hospital stays; nearly one-third had CDI as the principal diagnosis. Unfortunately, patients with CDI hospital stays were more severely ill than hospitalized patients in general, with 9.1% of CDI stays ending in death versus less than 2% for all other inpatients. Life-threatening conditions such as dehydration, septicemia, septic shock, renal failure, and hypoalbuminemia have been identified as potential complications of CDI by administrative data. The mean hospital LOS for a patient with CDI in US hospitals was 13 days, with a mean cost of $24,400 for all listed diagnoses ($8.2 billion overall).[73]

Antimicrobial Stewardship and Infection Prevention

CDI poses an inherent challenge to infection-prevention programs/ASPs, in that it exists in 2 forms: the vegetative form, which is found primarily within the GI tract, where it is inhibited by GI acid. However, once outside the GI tract the environment induces formation of spores, creating a form that is resistant to gastric acid, routine disinfectants, and hand sanitizers.[71] Proton pump inhibitors (PPIs) may result in an increased risk for CDI due to their inhibition of stomach acid.[74-76]

Epidemiology and infection-prevention departments are responsible for performing CDI surveillance; in many US states, health care facility–onset disease (ie, a positive CDI test specimen collected >3 days after admission or on/after hospital day 4) is publicly reportable. CMS also has determined that this will be a national reporting requirement as of January 2013. Health care facility–onset disease represents the minimum surveillance category for health care organizations to collate, but it often represents less than 50% of the total CDI burden within hospitals.[77] All CDI surveillance categories are tabulated at OSUWMC, and cases of health care facility–onset CDI and cases of other potentially preventable events (ie, central line–associated BSIs, VAPs, and selected surgical site infections) also are shared with administrative leadership as a metric on the OSUWMC quality scorecard each month.

With the recognition of increasing incidence and severity of CDI, obtaining testing results as rapidly as possible is helpful. Numerous rPCR tests have become available to shorten the time to diagnosis from 2 to 3 days (ie, cytotoxin assay) to hours.[78,79] Earlier CDI test

results lead to earlier treatment and more timely isolation to lessen potential cross transmission. Unfortunately, with implementation of the more sensitive, yet timely test, health care facility–onset cases have increased by approximately 40%, which also has been noted in other organizations.[80] When the rPCR (Cepheid Xpert C. difficile®) testing was implemented, OSUWMC's microbiology lab continued calling clinicians with positive results. In a cohort of its first 68 patients, metronidazole was consistently used as first-line therapy versus vancomycin, regardless of severity of CDI illness.[81] ID pharmacists now make follow-up calls to optimize anti-CDI therapy based on disease severity[82]; this study is ongoing to assess a larger number of patients. Recently, a small community hospital reported results from its program's approach to improving the management of patients with *C. difficile*.[83] Their Pharmacy and Therapeutics Committee approved a policy authorizing pharmacists to switch metronidazole to vancomycin if the patient had severe CDI.

Additional ASP initiatives at OSUWMC include a review of order sets with a PPI. Physician stakeholders were asked to re-evaluate the order set and remove PPIs unless they were absolutely necessary. Patients receiving more than 3 antimicrobials per day are being reviewed to assess for de-escalation or discontinuation, based on data by Stevens et al assessing the cumulative risk for antibiotic exposure over time.[84]

Infection-prevention goals for CDI mitigation include the following: early identification, contact isolation via barrier methods (ie, gown and gloves) for patients with symptoms of diarrhea (ie, 3 stools within 24 hours), and antibiotic exposure.[85] Dedicated equipment and patient-care items also are recommended for contact with patients and their environment, and private rooms are preferred. Meticulous compliance with hand-hygiene procedures before and after patient contact must occur. Use of soap and water for at least 15 seconds and decontamination of the environment with bleach in a 1:10 dilution is recommended in hyperendemic settings and outbreaks. Frequent re-education to stress these evidence-based guidelines is important to foster a culture of awareness of the epidemiology surrounding CDI and served as the basis in Ohio for a statewide collaborative in 2009-2010.[86]

At OSUWMC, ID pharmacists, infection preventionists, hospital epidemiologists, and environmental services receive daily email reports from the Microbiology Department about every new case of CDI. Each day, messaging subsequently goes to the unit nurse manager and attending of record to reinforce isolation processes and educational material for staff and family. Environmental services supervisors validate housekeeper cleaning with a fluorescent marker (Dazo, Ecolab Healthcare) following room cleaning to assure all "high-touch surfaces" are appropriately disinfected. OSUWMC plans to implement multiple ultraviolet emitters in each patient room to augment its current disinfection program.

Curtailing cross transmission of CDIs is OSUWMC's intent, but avoiding the diagnosis in the first place is the overarching global aim. CDI is inherently linked to antibiotics, the "lifesavers" that have been handed out at times "like candy" over the past few decades. Reversing cavalier use of antimicrobials represents the next laudable goal.

Conclusion

Opportunities for contributions by all members of the ASP to improve patient care are numerous, as outlined above. ASPs, however, should not justify their existence solely by curtailing antimicrobial costs. They should focus on appropriate empirical therapy based on local data, timely identification of pathogens to guide de-escalation, and avoidance of unnecessary antimicrobials. Collaboration of ASPs with clinicians will optimize patient management and should lead to favorable outcomes with a reduced risk for readmission.

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